(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 206 802 B1**

(12) # EUROPEAN PATENT SPECIFICATION

(45) Date of publication of patent specification: **01.09.93**

(51) Int. Cl.[5]: **C07D 215/48**, C07D 401/04, C07D 241/44, C07D 215/60, C07D 241/52, A61K 31/47, A61K 31/495, //C07D215/12, C07D215/18,C07D215/04

(21) Application number: **86304820.3**

(22) Date of filing: **23.06.86**

(54) **Substituted quinoline derivatives.**

(30) Priority: **24.06.85 NZ 212525**

(43) Date of publication of application:
30.12.86 Bulletin 86/52

(45) Publication of the grant of the patent:
01.09.93 Bulletin 93/35

(84) Designated Contracting States:
AT BE CH DE FR GB IT LI LU NL SE

(56) References cited:
EP-A- 0 098 098
EP-A- 0 172 744
DE-B- 2 009 894

(73) Proprietor: **CANCER RESEARCH CAMPAIGN TECHNOLOGY LIMITED**
Cambridge House 6-10 Cambridge Terrace
Regent's Park
London NW1 4JL(GB)

(72) Inventor: **Atwell, Graham John**
37 Hawkins Street
Meadowbank, Auckland 5(NZ)
Inventor: **Denny, William Alexander**
165 Gossamer Drive
Pakuranga, Auckland(NZ)
Inventor: **Rewcastle, Gordon William**
24 Rothery Road
Manurewa, Auckland(NZ)
Inventor: **The other inventors have agreed to waive their entitlement to designation**

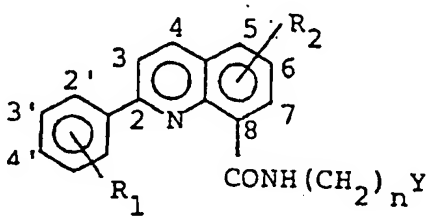
(74) Representative: **Senior, Janet et al**
Abel & Imray Northumberland House 303-306 High Holborn
London WC1V 7LH (GB)

EP 0 206 802 B1

Description

The present invention relates to novel 2-phenylquinoline derivatives having antitumour and antibacterial activity, to methods of preparing the novel compounds, and to their use as antibacterial and antitumour agents. The present invention also relates to novel compounds useful as intermediates in the preparation of the 2-phenylquinoline derivatives of the invention.

In one aspect the present invention relates to the novel class of substituted quinolines represented by the general formula (I):



(I)

where each of R_1 and R_2 separately represents H or one of the groups lower alkyl, halogen, CF_3, CN, SO_2CH_3, NO_2, OH, NH_2, $NHSO_2R_3$,$NHCOR_3$, $NHCOOR_3$, OR_3, SR_3, NHR_3 or NR_3R_3 (where R_3 is lower alkyl optionally substituted with hydroxy, lower alkoxy or an amino function), or may represent the substitution of an aza (-N=) group for one of the methine (-CH=) groups in the respective carbocyclic ring, or R_1 may represent, at positions 2', 3' or 4' only, a phenyl ring optionally further substituted with one of the groups lower alkyl, halogen, CF_3, CN, SO_2CH_3, NO_2, OH, NH_2, $NHCOR_3$, $NHCOOR_3$, OR_3, SR_3, NHR_3 or NR_3R_3 (where R_3 is lower alkyl optionally substituted with hydroxy, lower alkoxy or an amino function);
Y represents NR_4R_5, where each of R_4 and R_5 separately is H or (C_1-C_5)-alkyl optionally substituted with hydroxy, lower alkoxy or an amino function, or R_4 and R_5 together with the nitrogen atom to which they are attached form a 5- or 6-membered heterocyclic ring optionally containing a further hetero atom; and
n is from 2 to 6;
and the acid addition salts and 1-N-oxides thereof.

An amino function as substituent of a lower alkyl radical represented by R_3, R_4 and/or R_5 may be unsubstituted or, for example, substituted by one or two lower alkyl groups (where lower alkyl has the meaning given below), especially by one or two methyl groups. Thus, for example, an amino substituent of a lower alkyl radical represented by R_3, R_4 and/or R_5 may be NH_2, $NHCH_3$ or $N(CH_3)_2$.

A lower alkoxy group as substituent of a lower alkyl radical reprsented by R_3, R_4 and/or R_5 has 1 to 5 carbon atoms, and is especially a methoxy group.

A heterocyclic radical represented by R_4 and R_5 and the nitrogen atom to which they are attached may, if desired, contain an additional hetero atom and is 5-or 6-membered. An example is a morpholino group.

When R_1 R_2, R_3, R_4 or R_5 represent or contain as substituent lower alkyl, the group contains from 1 to 5 carbon atoms. Examples of lower alkyl optionally substituted with hydroxy, lower alkoxy or an amino function include lower alkyl optionally substituted with hydroxy, amino, methylamino, dimethylamino and O-methyl.

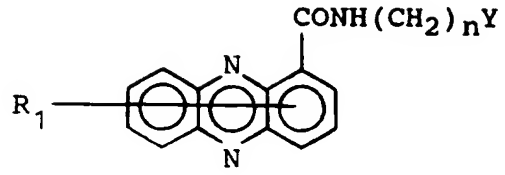
In a NR_3R_3 group the two R_3 substituents may be the same or different, but are preferably the same.

A preferred class of compound of the above formula (I) is that where R_1 represents one of aza, halogen, NO_2, or OCH_3, R_2 represents H, Y represents $N(CH_3)_2$ and n is 2.

The compounds of formula (I) have antibacterial and antitumour activity, and are useful as antibacterial and antitumour agents.

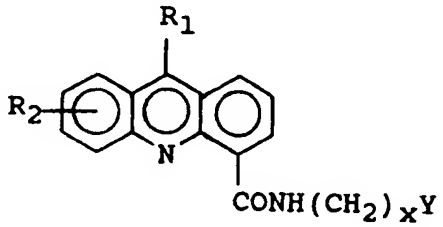
The compounds of formula (I) form pharmaceutically acceptable addition salts with both organic and inorganic acids. Examples of suitable acids for salt formation are hydrochloric, sulphuric phosphoric, acetic, citric, oxalic, malonic, salicylic, malic, fumaric, succinic, ascorbic, maleic, methanesulphonic.

Compounds of the general formula



in which
n and Y have the meanings given for formula I above and inter alia R_1 represents H or up to three substituents selected from lower alkyl, lower alkyl substituted by hydroxy, amino and/or ether (such as alkoxy) functions, OH, SH, OCH_2Ph, OPh, NO_2, halogen, CF_3, amino, $NHSO_2R_2$, $NHCOR_2$, $NHCOOR_2$, OR_2 and SR_2, where R_2 represents lower alkyl unsubstituted or substituted by hydroxy, amino and/or ether functions,
and their use as antitumour and antibacterial agents have been disclosed in EP 172744A.

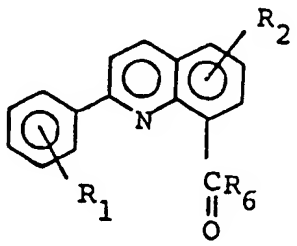
Compounds of the general formula



in which
x has the same meaning as n above,
Y represents $C(NH)NH_2$, $NHC(NH)NH_2$ or NR_4R_5, where each of R_4 and R_5 is H or lower alkyl optionally substituted with hydroxy and/or amino groups,
R_1 represents H, CH_3 or NHR_3, where R_3 is H, $COCH_3$, SO_2CH_3, COPh, SO_2Ph or lower alkyl optionally substituted with hydroxyl and/or amino groups,
R_2 represents H or up to two of the groups CH_3, OCH_3, halogen,CF_3, NO_2, NH_2, $NHCOCH_3$ and $NHCOOCH_3$ placed at positions 1-3 and 5-8,
are disclosed in EP 98098A and also have antitumour properties.

Neither of the European specifications mentioned discloses compounds having a substituted quinoline structure.

The compounds of the present invention of general formula (I) and the acid addition salts and 1-N-oxides thereof may be prepared for example by a process which comprises coupling a substituted quinoline of the general formula (II):



(II)

where R_1 and R_2 are as defined above and R_6 represents Cl, Br, OC_6H_4-p-NO_2, O-(1-N-benzotriazole), 1-N-imidazole, or an O-(2-N-methylpyridinium) salt or the 1-N-oxide thereof, with a primary alkyl amine of the general formula (III):

$NH_2(CH_2)nY$ (III)

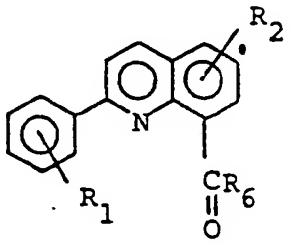
where n and Y are as defined above and, if desired, converting a compound of the invention into another such compound, for example a compound of formula (I) into an acid addition salt thereof, or vice versa

The coupling reaction is desirably performed in an anhydrous solvent (e.g. chloroform, dimethylsulphoxide or N-methylpyrrolidone, but preferably dichloromethane or dimethylformamide) preferably buffered with a tertiary amine (e.g. triethylamine). The reaction is conveniently performed at temperatures in the range of from 0 °C to 50 °C, with the preferred temperature being 20 °C.

The acid addition salts of the compounds of formula (I) are prepared by contacting the free base form with an equivalent amount of the desired acid in the conventional manner. The free base forms may be regenerated by treating the salt form with a base. For example, dilute aqueous base solutions may be utilized. Dilute aqueous potassium hydroxide, potassium carbonate, ammonia, and sodium bicarbonate solutions are suitable for this purpose. The free base forms differ from their respective salt forms somewhat in certain physical properties such as solubility in polar solvents but the salts are otherwise equivalent to their respective free base forms for the purposes of the invention.

The primary alkyl amines of the general formula (III) are known compounds and are commercially available or preparable by methods described in the literature. Examples of such compounds include N,N-dimethyl-1,2-ethanediamine (N,N-dimethylethylenediamine), N,N-diethyl-1,2-ethanediamine, N,N-dimethyl-1,3-propanediamine, N,N-dimethyl-1, 4-butanediamine, N,N-dimethyl-1,5-pentanediamine, N-(2-hydroxyethyl)-1,2-ethanediamine, (2-(2-aminoethylamino)-ethanol), N-methyl-N-(2-hydroxyethyl)-1,2-ethanediamine, 2-aminoethylguanidine $NH_2(CH_2)_2NHC(NH)NH_2$, and 3-aminopropionamidine $NH_2(CH_2)_2C(NH)NH_2$. The two last-mentioned compounds may be prepared according to P.L. Barker, P.L. Gendler and H. Rapoport, J.Ora.Chem., 46, 2455 (1981).

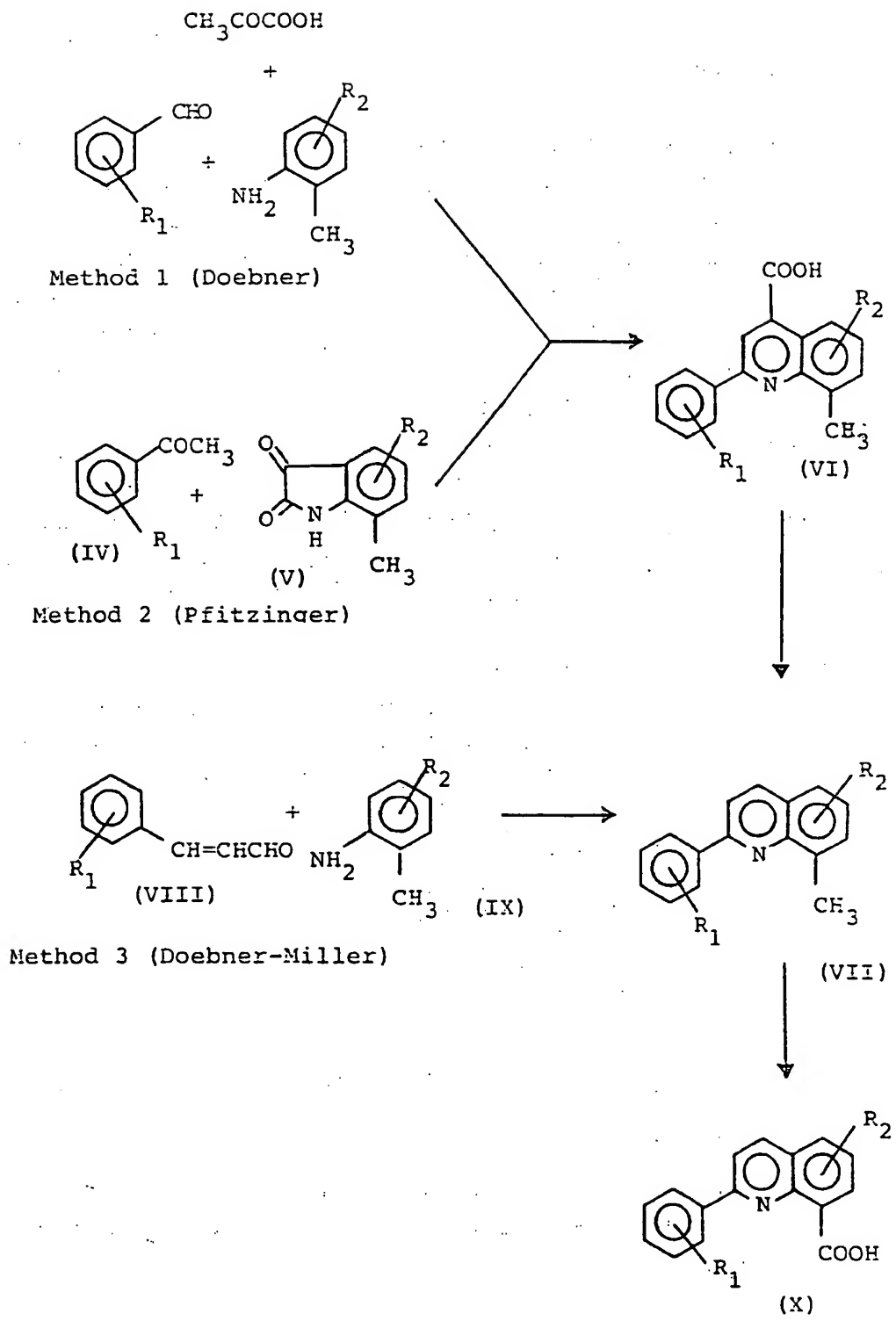
The substituted quinolines of formula (II) are novel compounds useful as intermediates in the preparation of the compounds of formula (I) and accordingly, the present invention also provides the compounds represented by the general formula (II):



(II)

where R_1, R_2 and R_6 are as defined above, and the 1-N-oxides thereof.

Substituted quinoline acids, which are compounds of general formula (II) where R_6 is OH, may be prepared by the processes outlined in Scheme I:



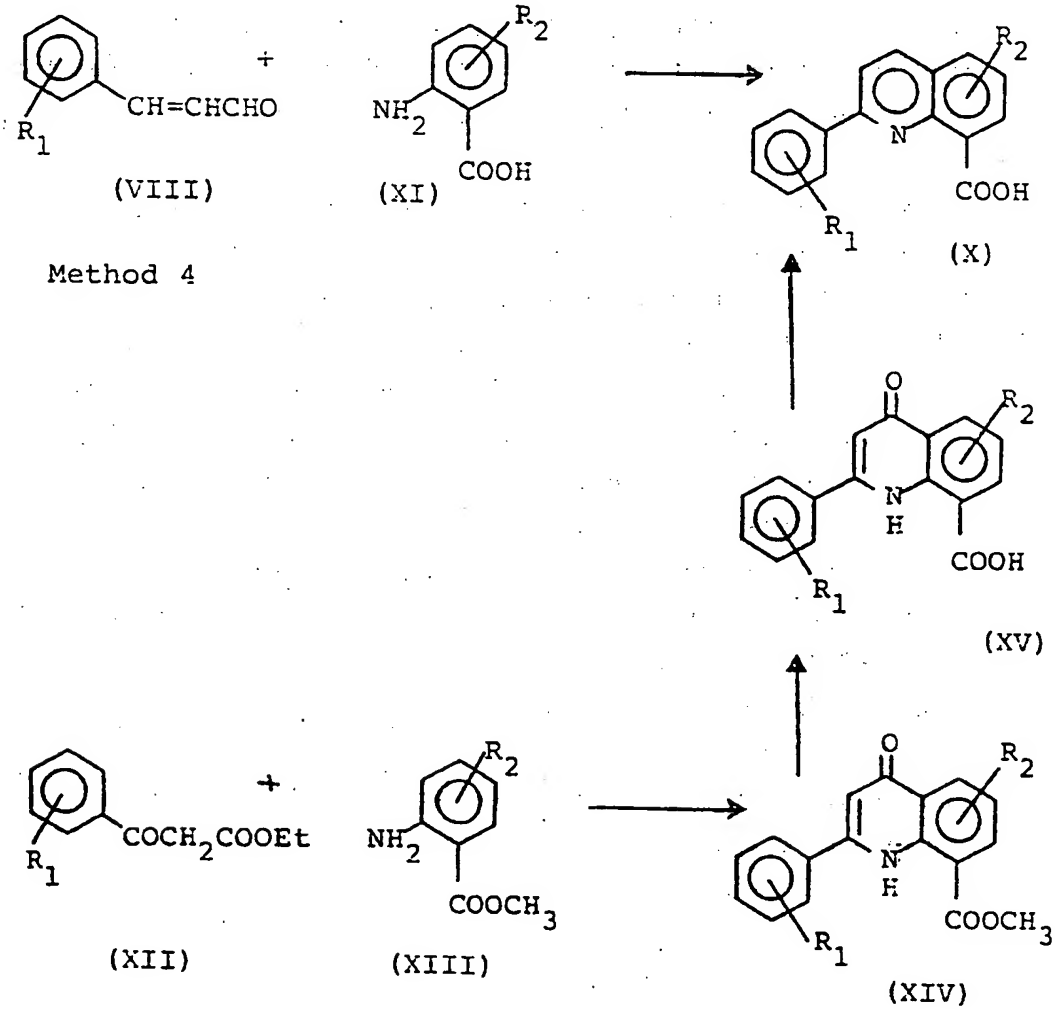
SCHEME I

In Scheme I each of R_1 and R_2 separately represents H or one of the groups halogen, CF_3, SO_2CH_3, NO_2 or OR_3, where R_3 is defined as for formula (I) or represents the substitution of an aza (-N=) group for one of the methine (-CH=) groups of the respective carbocyclic ring.

Condensation of aromatic aldehydes and o-toluidines together with pyruvic acid (Method I; Doebner reaction) provides 8-methyl-2-phenylquinoline-4-carboxylic acids (VI). An alternative but related preparation

of these compounds is via condensation of acetophenones (IV) with 7-methylisatins (V) (Method 2; Pfitzinger reaction). Copper-catalyzed decarboxylation of the acids (VI) provides the methylphenylquinolines (VII), which can also be prepared by condensation of cinnamaldehydes (VIII) with orthotoluidines (IX) (Method 3; Doebner-Miller reaction). Oxidation of the methyl group (using, for example, SeO_2 or H_2SO_4/CrO_3) then gives the desired 2-phenylquinoline-8-carboxylic acids (X) in moderate yields.

Substituted quinoline acids of general formula (II) where R_6 is OH may also be prepared by the processes outlined in Scheme II:



SCHEME II

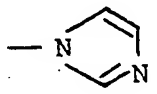
In Scheme II, R_1 and R_2 are as defined for formula (I).

Direct condensation of cinnamaldehydes (VIII) with anthranilic acids (XI) give the desired acids (X) in low yields (Method 4). Condensation of benzoylacetates (XII) with methyl anthranilates (XIII) (Method 5) gives good yields of the quinolones (XIV). Hydrolysis to (XV) followed by reduction with Al/Hg amalgam then provides the desired 2-phenylquinoline-8-carboxylic acids (X).

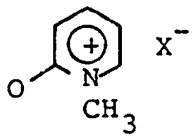
Reaction of the substituted quinoline acids (X) where R_6 represents OH (obtained by the methods outlined in Schemes I and II, or by any other method) with a suitable halogen reagent (e.g. PCl_5, $POCl_3$, but preferably $SOCl_2$) provides compounds of formula (II) where R_6 is Cl. Similar reaction of compounds of general formula (X) with $POBr_3$ or preferably $SOBr_2$ provides compounds of formula (II) where R_6 is Br.

Reaction of the substituted quinoline acids (X) with tris(4-nitrophenyl)phosphite in pyridine gives the 4-nitrophenylester derivatives (II) where R_6 is OC_6H_4-p-NO_2 (B. F. Cain, G. J. Atwell and W. A. Denny, J.Med.Chem., 20,987 (1977)).

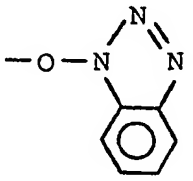
Reaction of the substituted quinoline acids (X) with 1,1'-carbonyldiimidazole in DMF or N-methylpyrrolidone gives the imidazolide derivatives of formula (II) where R_6 is 1-N-imidazole i.e.



Reaction of the substituted quinoline acids (X) with 2-chloro-N-methylpyridinium salts in DMF or N-methylpyrrolidone gives the 2-N-methylpyridinium salt esters of formula (II) where R_6 is an O-(2-N-methylpyridinium) salt, i.e.

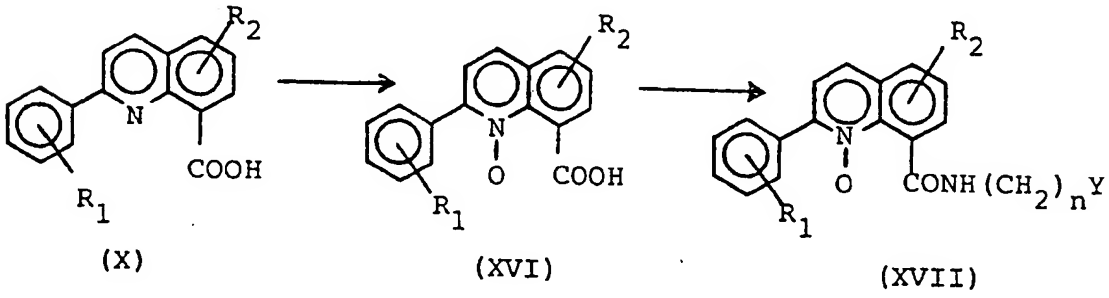


Reaction of the substituted quinoline acids (X) with bis(1-N-benzotriazole)carbonate in DMF or N-methylpyrrolidone gives the 1-N-benzotriazole esters of formula (II) where R_6 is O-(1-N-benzotriazole), i.e.



The compounds of general formula (II) where R_6 is as defined above are then coupled with suitable primary amines of formula (III) as described above to provide compounds of general formula (I).

The 1-N-oxides of the compounds of formula (I) may be prepared by the process outlined in Scheme III:



SCHEME III

In Scheme III, R_1, R_2, Y and n are as defined above for formula (I).

Oxidation of the substituted quinoline acids (X) with metachloroperbenzoic acid in chloroform or H_2O_2 in acetic acid provides the 1-N-oxide derivatives (XVI) which can be elaborated by the previously described methods to the desired products (XVII).

As will be appreciated, free bases/acids shown in the specification may, if appropriate, be in the form of salts, and compounds may be used in the form of their N-oxides if appropriate.

The following Tables I and II set out physical data for 26 compounds within the general formula (I), representative of it, and preparable by the processes of the invention. In Table I the following terms and abbreviations are used:

Mp melting point of the reported acid addition salt in °C,

Rm a measure of the compound's liphophilic-hydrophilic balance from reversed phase partition chromatography. Rm is linearly related to partition coefficients obtained in the 1-octanol/water system.

TABLE I

No.	R_1	R_2	n	Y	Mp(°C)	Rm
1	H	H	2	$N(CH_3)_2$	114-116	-0.01
2	H	H	3	$N(CH_3)_2$	214-216	0.06
3	H	H	4	$H(CH_3)_2$	208-209	0.14
4	H	H	5	$N(CH_3)_2$	171-174	0.21
5	H	H	2	$NH(CH_2)_2OH$	190-193	
6	H	H	2	N Morpholide	206-209	
7	2'-aza	H	2	$N(CH_3)_2$	168-170	-1.43
8	2'-Cl	H	2	$N(CH_3)_2$	169-171	0.15
9	3'-aza	H	2	$N(CH_3)_2$	249-252	-0.58
10	3'-Cl	H	2	$N(CH_3)_2$	110-111	0.05
11	3'-OCH_3	H	2	$N(CH_3)_2$	118-120	
12	4'-aza	H	2	$N(CH_3)_2$	235-237	-0.87
13	4'-F	H	2	$N(CH_3)_2$	133-136	
14	4'-Cl	H	2	$N(CH_3)_2$	250-251	0.05
15	4'-Br	H	2	$N(CH_3)_2$	123-124	
16	4'-I	H	2	$N(CH_3)_2$	118-119	
17	4'-Ph	H	2	$N(CH_3)_2$	180-183	
18	4'-OCH_3	H	2	$N(CH_3)_2$	200-201	-0.16
19	4'-OH	H	2	$N(CH_3)_2$	270-273	-0.33
20	4'-NO_2	H	2	$N(CH_3)_2$	244-245	-0.18
21	4'-NH_2	H	2	$N(CH_3)_2$	116-120	-0.76
22	4'-$NHCOCH_3$	H	2	$N(CH_3)_2$	160-164	
23	4'-$NHSO_2CH_3$	H	2	$N(CH_3)_2$	274-275	-0.38
24	H	5-Cl	2	$N(CH_3)_2$	245-246	
25	H	6-NO_2	2	$N(CH_3)_2$	280-282	

TABLE II

ELEMENTAL ANALYSES FOR THE COMPOUNDS OF TABLE I

No	Formula	MW	Found				Calculated			
			C	H	N	Cl	C	H	N	Cl
1	$C_{20}H_{21}N_3O.2HCl$	392.3	61.5	6.0	10.7	17.9	61.2	5.9	10.7	18.1
2	$C_{21}H_{23}N_3O.2HCl$	406.3	62.7	6.6	10.4		62.1	6.2	10.3	
3	$C_{22}H_{25}N_3O.HCl$	383.92	68.9	6.5	10.8	9.4	68.8	6.8	10.9	9.2
4	$C_{23}H_{27}N_3O.HCl$	397.94	69.1	7.0	10.5	9.2	69.4	7.1	10.6	8.9
5	$C_{20}H_{21}N_3O_2.2HCl$	408.33	58.7	5.5	10.2	17.2	58.8	5.7	10.3	17.4
6	$C_{22}H_{23}N_3O_2.2HCl$	434.37	60.5	5.9	9.9		60.8	5.8	9.7	
7	$C_{19}H_{20}N_4O.2HCl$	393.32	58.1	5.5	14.1	17.9	58.0	5.6	14.2	18.0
8	$C_{20}H_{20}ClN_3O.HCl$	390.31	61.4	5.4	10.7		61.5	5.4	10.8	
9	$C_{19}H_{20}N_4O.2HCl$	393.32	58.1	5.9	14.4	18.3	58.0	5.6	14.2	18.0
10	$C_{20}H_{20}ClN_3O$	353.85	68.1	5.5	11.9	10.0	67.9	5.7	11.9	10.0
11	$C_{21}H_{23}N_3O_2.2HCl.H_2O$	440.38	57.0	6.3	9.5	16.0	57.3	6.2	9.5	16.1
12	$C_{19}H_{20}N_4O.2HCl$	393.32	58.0	5.6	14.2	18.0	58.0	5.6	14.2	18.0
13	$C_{20}H_{20}FN_3O.2HCl$	410.33	58.4	5.4	10.1	18.0	58.5	5.4	10.2	17.3
14	$C_{20}H_{20}ClN_3O.HCl$	390.31	61.4	5.3	10.9		61.5	5.4	10.8	
15	$C_{20}H_{20}BrN_3O$	398.35	60.4	4.9	10.8		60.3	5.1	10.6	
16	$C_{20}H_{20}N_3OI$	445.29	54.0	4.3	9.2		53.9	4.5	9.4	
17	$C_{26}H_{25}N_3O.2HCl$	468.43	66.9	6.0	8.9	15.2	66.7	5.8	9.0	15.1
18	$C_{21}H_{23}N_3O_2.2HCl$	422.36	59.8	6.3	10.3	16.8	59.7	6.0	10.0	16.8
19	$C_{20}H_{21}N_3O_2.2HBr$	497.33	48.0	4.5	8.8	31.9(Br)	48.3	4.7	8.5	32.2(Br)
20	$C_{20}H_{20}N_4O_3.HCl$	400.87	60.2	5.6	13.9	9.0	59.9	5.3	14.0	8.9
21	$C_{20}H_{22}N_4O.2HCl$	407.35	58.7	4.6	13.2		59.0	5.9	13.7	
22	$C_{22}H_{24}N_4O_2.2HCl$	449.39	59.1	6.1	12.5	15.9	58.8	5.8	12.5	15.8
23	$C_{21}H_{24}N_4O_3S.2HCl$	486.24	51.8	5.4	11.2	14.9	52.0	5.4	11.5	14.6
24	$C_{20}H_{20}ClN_3O.HCl$	390.32	61.4	5.4	10.7	18.2	61.5	5.4	10.8	18.2
25	$C_{20}H_{20}N_4O_3.HCl$	400.87	59.9	5.4	14.1	9.1	60.0	5.3	14.0	8.8

The following Examples illustrate the preparation of compounds represented by the general formula (I)

EXAMPLE A

Preparation of Compound 1 of Table I by Method 1 of Scheme I

8-Methyl-2-phenylquinoline-4-carboxylic acid (VI; $R_1 = R_2 = H$)

A solution of 2-methylaniline (28g) in EtOH (50 mL) was added to a solution of pyruvic acid (33g) and benzaldehyde (28g) in EtOH (100 mL), and the mixture was heated under reflux for 3h and then allowed to cool overnight. The resulting solid was collected by filtration, washed well with cold EtOH and benzene and dried to give a product (13.4g) of acceptable purity. A sample crystallized from EtOH had mp 245-246 °C (lit. mp 245 °C Doebner and Giesecke, Ann. 1887, 242, 290).

8-Methyl-2-phenylquinoline (VII; $R_1 = R_2 = H$)

The above acid (9g) and Cu powder (0.7g) were heated at 280-290 °C until cessation of gas evolution. The cooled melt was extracted with boiling petroleum ether (bp40-60 °C) in the presence of charcoal, and the resulting solution was filtered and concentrated to give the crude product (7g) suitable for the next step. A sample was crystallized from petroleum ether as plates, mp 49-50 °C.

2-Phenylquinoline-8-carboxylic acid (X; $R_1 = R_2 = H$)

The above methylquinoline (5g) and SeO_2 (5.5g) were mixed and heated to 180-190 °C, when an exothermic reaction occurred which raised the internal temperature to 270-280 °C. The mixture was held at this temperature for 2 min, cooled, and the melt was extracted with hot $CHCl_3$. The resulting oil from this extraction was extracted with boiling dilute KOH and clarified by filtration. Excess AcOH then precipitated the crude acid, which was crystallized from EtOH to give the pure compound, mp 159-161 °C (Elderfield, R.C., Gensler, W. J., Orembry, T.H., Williamson T.A. and Weisl, H., J. Am. Chem. Soc., 1946, 68, 1589 record mp 158-159 °C).

Compound 1 of Table I

The above acid (1 equivalent) was suspended in dry DMF (10 mL/g) and treated with 1,1'-carbonyldiimidazole (1.5 equivalents) at 20-40 °C for 1h. The homogeneous mixture was cooled to 5 °C, treated with N,N-dimethylethylenediamine (2.5 equivalents), kept at 20 °C for 15 min and then most of the solvent was removed under reduced pressure. Addition of dilute aqueous Na_2CO_3 precipitated a solid which was extracted with CH_2Cl_2. The dried organic layer was evaporated and the residue of pure base was crystallized from MeOH-EtOAc-HCl to give the dihydrochloride, mp 114-116 °C Anal. ($C_{20}H_{21}N_3O.2HCl$) C,H,N,Cl.

Compounds 2 to 6 of Table I were similarly prepared from 2-phenylquinoline-8-carboxylic acid by substitution of the appropriate amine in the above procedure.

Example B

Preparation of Compound 7 of Table I by Method 2 of Scheme I

8-Methyl-2-(2-pridyl)quinoline-4-carboxylic acid (VI; R_1 = 2'-aza, $R_2 = H$)

A mixture of 2-acetylpyridine (IV; R_1 = 2-aza: 6.05g, 0.05 mol) and 7-methylisatin (V; $R_2 = H$: 8.52g, 0.053 mol) in 65mL of 50% EtOH-H_2O containing KOH (13g) was refluxed for 2h, then diluted with 50% EtOH-H_2O to obtain a homogeneous solution, filtered and acidified (HOAc). The resulting acid was collected, washed with 30% EtOH-H_2O and recrystallized from DMF-EtOH to provide the product (9.4g, 67%, mp. 319-320 °C. Anal. ($C_{16}H_{12}N_2O_2$) C,H,N.

Similar reactions using appropriately substituted acetophenones gave the 8-methyl-2-phenylquinoline-4-carboxylic acids (VI) listed in Table III.

8-Methyl-2-(2-pyridyl)quinoline (VII; R_1 = 2'-aza, R_2 = H)

The preceding quinoline acid (V; R_1 = 2'-aza, R_2-H; 7.0g) and Cu powder (0.5g) were heated at 280-290 °C until cessation of gas evolution. The cooled melt was extracted with boiling petroleum ether (bp 40-60 °C) in presence of charcoal and the filtered solution evaporated to provide the crude product (5.2g). A sample crystallized from petroleum ether (bp 40-60 °C) as plates, mp. 83-84 °C. Anal. ($C_{15}H_{12}N_2$) C,H,N.

Similar decarboxylations of the quinoline acids (VI) listed in Table III gave the 8-methyl-2-phenylquinolines (VII) listed in Table IV.

2-(2-pyridyl)quinoline-8-carboxylic acid (X; R_1 = 2'-aza,R2 = H)

The above methylquinoline (VII; R_1 = 2'-aza,R_2 = H: 3.5g) and SeO_2 (4.2g) were heated with mixing to 180-190 °C, when a violent exothermic reaction occurred and the temperature rose rapidly to 270-280 °C. The reaction mixture was held at this temperature for 2 min, then cooled and the melt extracted with hot $CHCl_3$. Evaporation left an oil which was extracted with boiling dilute aq.KOH (charcoal), clarified by filtration, partially neutralised with HOAc,and refiltered. Excess HOAc, was then added to precipitate the crude product. Crystallization of this material from benzene-petroleum ether and then EtOH afforded the pure quinoline acid (X) (1.44g, 36%) as needles, mp. 199-201 °C. Anal:($C_{15}H_{10}N_2O_2$) C,H,N.

Similar oxidations of the methylquinolines (VII) listed in Table IV gave the 2-phenylquinoline-8-carboxylic acids (X) listed in Table V.

Compound 7 of Table I.

The above acid (X; R_1 = 2'-aza, R_2 = H) was treated with 1,1'-carbonyldiimidazole and N,N-dimethylethylenediamine as described in Example A to give compound 7 as needles, mp 168-170 °C. Anal. ($C_{19}H_{20}N_4O.2HCl$) C,H,N,Cl.

Compounds 8 to 18 and 24 to 25 of Table I were similarly prepared from the 2-phenylquinoline-8-carboxylic acids (X) listed in Table V.

TABLE III

8-METHYL-2-PHENYLQUINOLINE-4-CARBOXYLIC ACIDS (VI)				
R_1	R_2	Mp(°C)	Formula	Analyses
2'-Cl	H	230-231	$C_{17}H_{12}ClNO_2$	C,H,N
3'-aza	H	250-252	$C_{16}H_{12}N_2O_2.1/2H_2O$	C,H,N
3'-Cl	H	272-274	$C_{17}H_{12}ClNO_2$	C,H,N,Cl
3'-OCH_3	H	210-211	$C_{18}H_{15}NO_3$	C,H,N
4'-aza	H	347-349	$C_{16}H_{12}N_2O_2$	C,H,N
4'-F	H	249-251	$C_{17}H_{12}FNO_2$	C,H,N,F
4'-Cl	H	253-255	$C_{17}H_{12}ClNO_2$	C,H,N
4'-Br	H	256-257	$C_{17}H_{12}BrNO_2$	C,H,N,Br
4'-I	H	276-278	$C_{17}H_{12}INO_2$	C,H,N,I
4'-Ph	H	237-239	$C_{23}H_{17}NO_2$	C,H,N
4'-OCH_3	H	242-244	$C_{17}H_{15}NO_3$	C,H,N
H	5-Cl	287-289	$C_{27}H_{12}ClNO_2$	C,H,N,Cl
H	6-NO_2	185-186	$C_{17}H_{12}N_2O_4$	C,H,N.

TABLE IV

8-METHYL-2-PHENYLQUINOLINES (VII)				
R_1	R_2	Mp(°C)	Formula	Analysis
2'-Cl	H	89- 91	$C_{16}H_{12}ClN$	C,H,N,Cl
3'-aza	H	54- 55	$C_{15}H_{12}N_2$	C,H,N
3'-Cl	H	58- 60	$C_{16}H_{12}ClN$	C,H,N
3'-OCH_3	H	67.5- 68	$C_{17}H_{15}NO$	C,H,N
4'-aza	H	77- 78	$C_{15}H_{12}N_2$	C,H,N
4'-F	H	70- 72	$C_{15}H_{12}FN$	C,H,N
4'-Cl	H	78- 78.5	$C_{16}H_{12}ClN$	C,H,N,Cl
4'-Br	H	84- 85	$C_{16}H_{12}BrN$	C,H,N,Br
4'-I	H	102-103	$C_{16}H_{12}IN$	C,H,N
4'-Ph	H	178-180	$C_{22}H_{17}N$	C,H,N
4'-OCH_3	H	85- 85.5	$C_{17}H_{15}N$	C,H,N
H	5-Cl	97- 98	$C_{16}H_{12}ClN$	C,H,N,Cl
H	6-NO_2	171-171.5	$C_{16}H_{12}N_2O_2$	C,H,N,Cl

TABLE V

2-PHENYLQUINOLINE-8-CARBOXYLIC ACIDS (X)				
R_1	R_2	Mp(°C)	Formula	Analysis
2'-Cl	H	251-252	$C_{16}H_1OClNO_2$	C,H,N,Cl
3'-aza	H	224-226	$C_{15}H_{10}N_2O_2$	C,H,N
3'-Cl	H	233-236	$C_{16}H_{10}ClNO_2$	C,H,N,Cl
3'-OCH_3	H	137-138	$C_{17}H_{13}NO_3$	C,H,N
4'-aza	H	255-257	$C_{15}H_{10}N_2O_2$	C,H,N
4'-F	H	214-215	$C_{16}H_{10}FNO_2$	C,H,N,F
4'-Cl	H	209-210	$C_{16}H_{10}ClNO_2$	C,H,N,Cl
4'-Br	H	226-227	$C_{16}H_{10}BrNO_2$	C,H,N,Br
4'-I	H	236-238	$C_{16}H_{10}INO_2$	C,H,N
4'-Ph	H	200-201	$C_{22}H_{15}NO_2$	C,H,N
4'-OCH_3	H	172-173	$C_{17}H_{13}NO_3$	C,H,N
H	5-Cl	241-242	$C_{18}H_{10}ClNO_2$	C,H,N,Cl
H	6-NO_2	268-269	$C_{16}H_{10}N_2O_4$	C,H,N

Example C

Preparation of Compound 20 of Table I by Method 3 of Scheme I

8-Methyl-2-(4-nitrophenyl)quinoline (VII : R_1 = 4'-NO_2, R_2 = H)

A mixture of 4-nitrocinnamaldehyde (VIII : R_1 = 4'-NO_2) (71g, 0.40 mol), 2-methylaniline (IX : R_2 = H (48g, 0.45 mol) and conc. HCl (150 mL) was stirred and heated in an oil bath at 140-150 °C for 5h. The hot acidic solution was decanted, and the remaining tar was extracted with hot conc. HCl (150 mL). The combined acid fractions were concentrated under reduced pressure and basified with ammonia and the resulting oil was extracted with $CHCl_3$. The crude product from evaporation of the $CHCl_3$ was crystallized, first as the methanesulfonate salt from boiling aqueous methanesulfonic acid, and then as the free base from petroleum ether (bp 100-120 °C) and finally from EtOAc to give pure product as pale yellow needles (8.1g), mp 117-117.5 °C. Anal. ($C_{16}H_{12}N_2O_2$) C,H,N.

This is a modification of the literature procedure for the preparation of 2-(4-nitrophenyl)quinoline.

2(4-Nitrophenyl)quinoline-8-carboxylic acid (X : R_1 = 4'-NO_2, R_2 = H)

A stirred solution of the above methylquinoline (2.3g) in conc. H_2SO_4 (25 mL) and water (40 mL) was heated to 90 °C and treated portionwise with CrO_3 (9.9g) at such a rate as to maintain the temperature below 105 °C. After completion of the reaction the mixture was diluted with water, and the resulting precipitate was collected, washed with water, dissolved in hot dilute aqueous KOH, and filtered. Slow addition of dilute aqueous AcOH precipitated impurities which were removed by filtration. Addition of excess AcOH then provided the required product. Two recrystallizations from AcOH/MeOH afforded the pure acid as pale yellow needles (64% yield), mp 272-274 °C. Anal. ($C_{16}H_{10}N_2O_4$) C,H,N.

Compound 20 of Table I

The above acid was treated with 1,1'-carbonyldiimidazole and N,N-dimethylethylenediamine as described in Example A to give compound 20 as the monohydrochloride, mp 244-245 °C. Anal. ($C_{20}H_{20}N_4O_3HCl$) C,H,N,Cl.

Example D

Preparation of Compound 1 of Table I by Method 4 of Scheme II

2-Phenylquinoline-8-carboxylic Acid (X ; R_1 = R_2 = H)

A mixture of conc. H_2SO_4 (45 mL), water (5 mL), AcOH (5 mL), anthranilic acid (XI ; R_2 = H) (20.5g) and H_3AsO_4 (80% w/w; 32g) was heated with stirring to 105 °C, and then treated with cinnamaldehyde (VIII ; R_1 = H) (25g) at the rate which maintained the temperature at 105-110 °C. The reaction mixture was stirred for a further 3h at 110-115 °C, then cooled and strongly basified with aqueous KOH. The aqueous layer was decanted from a quantity of tar, washed with $CHCl_3$ and then acidified with AcOH. The resulting precipitate was chromatographed on SiO_2 and eluted with a gradient of MeOH in CH_2Cl_2 to give a low yield of the desired acid, mp 160-161 °C, identical in all respects to the compound obtained in Example A. This compound was elaborated to compound 1 of Table I by the method outlined in Example A.

Example E

Preparation of Compound 1 of Table I by Method 5 of Scheme II

8-Methoxycarbonyl-2-phenyl-4(1H)-quinolone (XIV ; R_1 = R_2 = H)

A mixture of methyl anthranilate (XIII ; R_2 = H : 75.6g, 0.50 mol) and ethyl benzoylacetate (XII ; R_1 = H : 96g, 0.50 mol) in benzene (400 mL) containing methanesulfonic acid (0.5ml) was refluxed for 36h under a Dean-Stark water entrainment head. After concentration to half volume, petroleum ether was added to precipitate a white solid (64g) that was collected and added over a 15 min period to refluxing Dowtherm A (255 °C) The cooled mixture was diluted with benzenepetroleum ether and the resulting solid was collected, washed with benzene-petroleum ether and dried, yielding the crude quinolone (45.8g). A sample crystallized from benzene as colourless prisms, mp. 216-217 °C. Anal. ($C_{17}H_{13}NO_3$) C,H,N.

2-Phenyl-4(1H)-quinolone-8-carboxylic acid (XV ; R_1 = R_2 = H)

A mixture of the above ester (XIV ; R_1 = R_2 = H) (40g) and 500 mL of 50% EtOH-H_2O containing KOH (27g) was refluxed for 2h. Enough 30% EtOH-H_2O was added to dissolve the precipitated potassium salt of the product in the hot and then the filtered solution was slowly acidified with HCl-EtOH so as to obtain the quinolone acid in granular form. This material was collected, washed well with 30% EtOH-H_2O and benzene and dried, providing product (34.9g, 98%) essentially pure by T.L.C. A sample crystallized from DMF-EtOH-H_2O as prisms, mp. 304-306 °C . Anal.($C_{16}H_{11}NO_3$) C,H,N.

2-Phenylquinoline-8-carboxylic acid (X ; R_1 = R_2 = H)

A hot stirred solution of the preceding quinolone acid (XV; R_1 = R_2 = H; 5.5g) in 300 mL of 50% EtOH-H_2O containing KOH (1.4g) was treated in portions with aluminium foil that had been pretreated by

immersion in a 9% ethanolic solution of $HgCl_2$. Following completion of the reaction the mixture was filtered, acidified (HCl), treated in the hot with $FeCl_3$ (5g) and refluxed for 30 min. Neutralisation with aq. KOAc precipitated solids that were collected and extracted with hot aq KOH. Acidification (HOAc) of the filtered extract provided crude product that was recrystallized twice from bezene-petroleum ether providing T.L.C. homogeneous material (15%), mp 159-161 °C identical to that prepared in Example A.

Compound 1 of Table I

Treatment of the quinoline acid (X ; $R_1 = R_2 = H$) with 1.1'-carbonyldiimidazole and N,N-dimethylethylenediamine by the method described in Example A gave compound 1 of Table I as the dihydrochloride, mp. 114-116 °C.

Example F

Preparation of Compound 25 by Method 1 of Scheme I

8-Methyl-6-nitro-2-phenylquinoline-4-carboxylic acid (VI ;$R_1 = H$, $R_2 = 6\text{-}NO_2$)

Methanesulfonic acid (7.1 mL, 0.11 mol) was stirred into a mixture of 2-methyl-4-nitroaniline (15.2g, 0.1 mol), benzaldehyde (10.6g, 0.1 mol) and pyruvic acid (8.8g, 0.1 mol) and, following an initial exotherm was heated at 100 °C for 3h. The mixture was cooled and triturated with water and the resulting tar was extracted with hot dilute aqueous Et_3N. The solution was treated with charcoal and filtered and the filtrate was acidified with HCl to give the crude product. Two crystallizations from EtOH gave the pure acid as pale yellow prisms (4.6g, 45% yield), mp 185-186 °C. Anal.($C_{17}H_{12}N_2O_4$) C,H,N.

This is a modification of a procedure described for the synthesis of 8-nitro-2-phenylquinoline-4-carboxylic acid (Buchman, E. R., McCloskey, C.M., Seneker, J.A. J. Am. Chem. Soc., 1947, 69, 380).

8-Methyl-6-nitro-2-phenylquinoline (VII ;$R_1 = H$, $R_2 = 6\text{-}NO_2$)

A mixture of the above acid (2g) and Cu powder (0.2g) in quinoline (10 mL) was heated to 230 °C for 15 min. The cooled mixture was diluted with water to precipitate the crude product, which was crystallized from MeOH, mp 171-171.5 °C.Anal. ($C_{16}H_{12}N_2O_2$) C,H,N.

6-Nitro-2-phenylquinoline-8-carboxylic acid (X : $R_1 = H$, $R_2 = 6\text{-}NO_2$)

The above quinoline was oxidized with SeO_2 as described in Example A to give the desired acid, mp 268-269 °C.Anal. ($C_{16}H_{10}N_2O_4$) C,H,N.

Compound 25 of Table 1

The above quinoline acid was treated with 1,1'-carbonyldiimidazole and N,N-dimethylethylenediamine as described in Example A to give compound 25 of Table I, mp 280-282 °C.Anal. ($C_{20}H_{20}N_4O_3 \cdot HCl$) C,H,N,Cl.

The compounds of general formula (I), and particularly the Examples listed in Tables I and II, have antitumour activity in both in vitro and in vivo test systems, as shown by the data of Table VI.

The following Table VI gives biological data for the compounds whose physical data has been given in Tables I and II. The abbreviations used in Table VI are :

No I.	The number given to the corresponding compound in Table
IC_{50}	The nanomolar concentration of drug which, when added to cultures of L1210 leukemia cells for 70h, reduces counted cell numbers to 50% of controls. Compounds with IC_{50} values higher than 2000 nanomolar are considered unlikely to show activity in vivo.
OD	The optimal drug dose (in milligrams per kilogram), administered intraperitoneally as a solution in 0.1ml of 30% v/v ethyl alcohol in water on days 1,5 and 9 after tumour inoculation. The drug is administered as a soluble acid addition salt.
ILSmax	The percentage increase in lifespan of treated animals over that of control animals injected with tumour alone. The average survival of control mice was 11 days (for P388 leukemia) and 17 days (for Lewis lung carcinoma) ILS values greater than 20% (P388 leukemia) and 40% (Lewis lung carcinoma) are considered statistically significant. Numbers in parentheses after ILS values indicate the number of long-term survivors (out of a group of 6).
Y	Implies a significant value of drug activity at the stated dose.
N	Implies no statistically significant activity.
P388	Is the P388 leukemia.
LL	Is the Lewis lung carcinoma.

Both of these tumour lines were obtained as frozen cell stocks from Mason Research Inc., USA and are passaged intraperitoneally in DBA/25 mice of either sex (P388) or subcutaneously in C57BL/65 mice of either sex (LL) according to the standard methods (Cancer Chemother. Reports.,3, Part 3, p9, 1972).

Groups of six mice (FI hybrids of DBA/2J male x C57BL/6J female) were injected intraperitoneally (P388) or intravenously (tail vein, LL) with 10^6 tumour cells on day 0. When given in this manner, P388 cells grow diffusely in the peritoneal cavity, whereas the Lewis lung cells form distinct solid tumour nodules in the lungs. Antitumour activity is determined by published methods (European J. Cancer, 19, pp.1607-1613, 1983).

TABLE VI

BIOLOGICAL ACTIVITY Of THE COMPOUNDS Of TABLE I							
No.	In vitro L1210(IC_{50})	P388 in vivo			LL in vivo		
		OD	ILS	Active	OD	ILS	Active
1	1300	100	91	Y	100	70(4)	Y
2	1140	100	71	Y	100	<40	N
3	680	100	93	Y	100	148(2)	Y
4	1300	150	<20	N	100	<40	N
5		65	<20	N			
6		150	<20	N			
7	1640	65	73(3)	Y	100	91	Y
8	8100	100	<20	N			
9	840	100	58	Y	100	55(2)	Y
10	1200	65	40	Y	100	<40	N
11	860	225	46	Y			
12	170	45	145(2)	Y	65	132(3)	Y
13		100	<20	N			
14	1170	100	52	Y	65	91(4)	Y
15	600	100	72	Y			
16		100	48	Y			
17	1290	100	<20	N			
18	1290nm	150	42	Y			
19	27	65	22	Y			
20	290	100	71	Y	65	85	Y
21	200	100	28	Y	100	65	Y
22	740	65	<20	N			
23	1330	65	<20	N			
24		150	63	Y			
25		150	63	Y			

It is clear from the data of Table VI that the 2-phenylquinoline derivatives of general formula (I) include compounds which are active antitumour agents, giving significant levels of life extension when tested against the P388 leukemia or Lewis lung carcinoma systems when given by intraperitoneal or intravenous injection, respectively, and/or significant inhibition of cultured L1210 leukemia cells in vitro. The compounds also show antitumour activity when given by oral and intravenous routes. In addition to high cytotoxicity towards cultured L1210 leukemia cells, they are active in a number of other cultured tumour cell lines, including those originating from human breast and colon tumours.The compounds of general formula (I) are thus indicated for use as antitumour agents.

The compounds also show antibacterial activity; specifically compounds 1 and 12 show in vitro activity against a number of bacterial cell lines. Thus the invention provides for the use of these compounds as antibacterial agents.

The present invention therefore also further provides a compound of formula (I) or a pharmaceutically acceptable addition salt or 1-N-oxide thereof, for use in the treatment of tumours, and in particular cancers.

The present invention further provides pharmaceutical compositions having antitumour activity and comprising at least one compound of general formula (I) or a pharmaceutically acceptable acid addition salt

or 1-N-oxide thereof, and one or more pharmaceutically acceptable carriers or diluents.

The active compounds may be orally administered, for example, with an inert diluent or with an assimilable edible carrier, or they may be enclosed in hard or soft shell gelatin capsules, or they may be compressed into tablets, or they may be incorporated directly with the food of the diet. For oral therapeutic administration, the active compounds may be incorporated with excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers and the like. Such compositions and preparations should contain at least 0.1% of active compound. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between about 2 and about 60% of the weight of the unit. The amount of active compound in such therapeutically useful compositions is such that a suitable dosage will be obtained. Preferred compositions or preparations according to the present invention are prepared so that an oral dosage unit form contains between about 5 and about 200 milligrams of active compound.

The tablets, troches, pills, capsules and the like may also contain the following : a binder such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, lactose or saccharin may be added or a flavouring agent such as peppermint, oil of wintergreen or cherry flavouring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets, pills or capsules may be coated with shellac, sugar or both. A syrup or elixir may contain the active compound, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavouring such as cherry or orange flavour. Of course, any material used in preparing any dosage unit form should be pharmaceutically pure and substantially non-toxic in the amounts employed. In addition, the active compounds may be incorporated into sustained-release preparations and formulations.

The active compounds may also be administered parenterally or intraperitoneally. Solutions of the active compound as a free base or pharmaceutically acceptable salt can be prepared in water suitably mixed with a surfactant such as hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), suitable mixtures thereof and vegetable oils. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersions and by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminium monostearate and gelatin.

Sterile injectable solutions are prepared by incorporating the active compound in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredients into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and the freeze-drying technique which yield a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

As used herein, "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions is contemplated. Supplementary active ingredients can also be incorporated into the compositions.

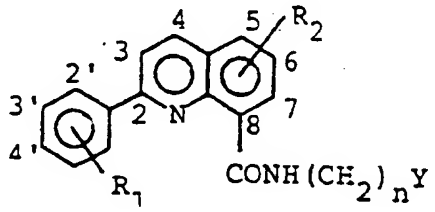
It is especially advantageous to formulate parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suitable as unitary dosages for the mammalian subjects to be treated; each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the novel dosage unit forms of the invention are dictated by and directly dependent on (a) the unique characteristics of the active material and the particular therapeutic effect to be achieved, and (b) the limitations inherent in the art of compounding such an active material for the treatment of disease in living subjects having a diseased condition in which bodily health is impaired as herein disclosed in detail.

The principal active ingredient is compounded for convenient and effective administration in effective amounts with a suitable pharmaceutically-acceptable carrier in dosage unit form as hereinbefore disclosed. A unit dosage form can, for example, contain the principal active compound in amounts ranging from about 0.1 to about 400 mg with from about one to about 30 mg being preferred. Expressed in proportions, the active compound is generally present in from about 0.1 to about 400 mg/ml of carrier. In the case of compositions containing supplementary active ingredients, the dosages are determined by reference to the usual dose and manner of administration of the said ingredients.

Claims

Claims for the following Contracting States: BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. A compound represented by the general formula (I)



(I)

where each of R_1 and R_2, which may be the same or different, represents H or one of the groups (C_1-C_5)-alkyl, halogen, CF_3, CN, SO_2CH_3, NO_2, OH, NH_2, $NHSO_2R_3$, $NHCOR_3$, $NHCOOR_3$, OR_3, SR_3, NHR_3 or NR_3R_3 (where R_3 represents (C_1-C_5)-alkyl optionally substituted with hydroxy, (C_1-C_5)-alkoxy or an amino function), or represents the replacement of one of the methine (-CH=) groups in the respective carbocyclic ring by an aza (-N=) group or, in the case of R_1, may represent, at positions 2', 3' or 4' only, a phenyl ring optionally substituted with one of the groups (C_1-C_5)-alkyl, halogen, CF_3 CN, SO_2CH_3, NO_2, OH, NH_2, $NHCOR_3$, $NHCOOR_3$, OR_3, SR_3, NHR_3 or NR_3R_3 (where R_3 represents (C_1-C_5)-alkyl optionally substituted with hydroxy, (C_1-C_5)-alkoxy or an amino function and where the two R_3 groups in NR_3R_3 may be the same or different);
Y represents NR_4R_5, where each
of R_4 and R_5, which may be the same or different, represents H or (C_1-C_5)-alkyl optionally substituted with hydroxy, (C_1-C_5)-alkoxy or an amino function, or R_4 and R_5 together with the nitrogen atom to which they are attached form a 5- or 6-membered heterocyclic ring optionally containing a further hetero atom; and
n is from 2 to 6;
or an acid addition salt or 1-N-oxide thereof.

2. A compound according to claim 1 where R_1 represents aza, halogen, NO_2, or OCH_3, R_2 represents H, Y represents $N(CH_3)_2$ and n is 2.

3. A compound according to claim 1 where R_1 and R_2 represent H, Y represents $N(CH_3)_2$ and n is 2.

4. A compound according to claim 1 where R_1 represents 2'-aza, R_2 represents H, Y represents $N(CH_3)_2$ and n is 2.

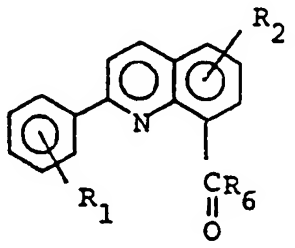
5. A compound according to claim 1 where R_1 represents 3'-aza, R_2 represents H, Y represents $N(CH_3)_2$ and n is 2.

6. A compound according to claim 1 where R_1 represents 3'-Cl, R_2 represents H, Y represents $N(CH_3)_2$ and n is 2.

7. A compound according to claim 1 where R_1 represents 4'-aza, R_2 represents H, Y represents $N(CH_3)_2$ and n is 2.

8. A compound according to claim 1 where R_1 represents 4'-Cl, R_2 represents H, Y represents $N(CH_3)_2$ and n is 2.

9. A process for the preparation of a compound represented by the general formula (I) as defined in claim 1, or an acid addition salt or 1-N-oxide thereof, which process comprises coupling a substituted quinoline of the general formula (II):



(II)

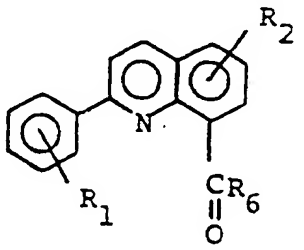
where R_1 and R_2 are as defined in claim 1 and R_6 represents Cl, Br, OC_6H_4-pNO_2, O-(1-N-benzotriazole), 1-N-imidazole or an O-(2-N-methylpyridinium) salt, or the 1-N-oxide thereof, with a primary alkyl amine of the general formula (III):

$NH_2(CH_2)n^Y$ (III)

where n and Y are as defined in claim 1 and, if desired, converting a compound of formula (I) into an acid addition salt thereof.

10. A process according to claim 9 wherein the coupling reaction of compound (II) with compound (III) is performed in an anhydrous solvent selected from chloroform, dimethylsulphoxide, N-methylpyrrolidone, dichloromethane and dimethylformamide, buffered with a tertiary amine.

11. A compound represented by the general formula (II)



(II)

where R_1 and R_2 are defined as in claim 1, and R_6 represents Cl, Br, OC_6H_4-p-NO_2, O-(1-N-benzotriazole), 1-N-imidazole, or an O-(2-N-methylpyridinium) salt, or the 1-N-oxide thereof.

12. A pharmaceutical composition which comprises at least one compound of the general formula (I) defined in claim 1, or a pharmaceutically acceptable acid addition salt or 1-N-oxide thereof, and one or more pharmaceutically acceptable carriers or diluents.

13. A pharmaceutical composition which comprises a compound according to any one of claims 2 to 8, or a pharmaceutically acceptable acid addition salt or 1-N-oxide thereof and one or more pharmaceutically acceptable carriers or diluents.

14. A compound of the general formula (I) as defined in claim 1, or a pharmaceutically acceptable acid addition salt or 1-N-oxide thereof, for use in the treatment of tumours.

15. A compound according to any one of claims 2 to 8, or a pharmaceutically acceptable acid addition salt or 1-N-oxide thereof for use in the treatment of tumours.

16. A compound of the general formula (I) as defined in claim 1, or a pharmceutically acceptable acid addition salt or 1-N-oxide thereof, for use as an anti-bacterial agent.

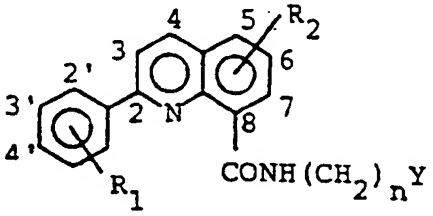
17. A compound according to any one of claims 2 to 8, or a pharmaceutically acceptable acid addition salt or 1-N-oxide thereof, for use as an anti-bacterial agent.

18. The use of a compound of the general formula (I) as defined in claim 1, or a pharmaceutically acceptable acid addition salt or 1-N-oxide thereof, for the manufacture of a medicament for use in the treatment of tumours.

19. The use of a compound of the general formula (I) as defined in claim 1, or a pharmaceutically acceptable acid addition salt or 1-N-oxide thereof, for the manufacture of a medicament for use as an anti-bacterial.

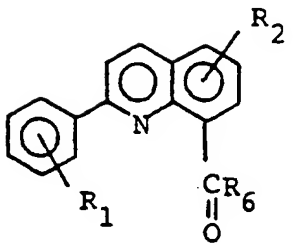
Claims for the following Contracting State: AT

1. A process for the preparation of a compound represented by the general formula (I):



(I)

where each of R_1 and R_2, which may be the same or different, represents H or one of the groups (C_1-C_5)-alkyl, halogen, CF_3, CN, SO_2CH_3, NO_2, OH, NH_2, $NHSO_2R_3$, $NHCOR_3$, $NHCOOR_3$, OR_3, SR_3, NHR_3 or NR_3R_3 (where R_3 represents (C_1-C_5)-alkyl optionally substituted with hydroxy, (C_1-C_5)-alkoxy or an amino function), or represents the replacement of one of the methine (-CH=) groups in the respective carbocyclic ring by an aza (-N=) group or, in the case of R_1, may represent, at positions 2', 3' or 4' only, a phenyl ring optionally substituted with one of the groups (C_1-C_5)-alkyl, halogen, CF_3, CN, SO_2CH_3, NO_2, OH, NH_2, $NHCOR_3$, $NHCOOR_3$, OR_3, SR_3, NHR_3 or NR_3R_3 (where R_3 represents (C_1-C_5)-alkyl optionally substituted with hydroxy, (C_1-C_5)-alkoxy or an amino function and where the two R_3 groups in NR_3R_3 may be the same or different);
Y represents NR_4R_5, where each of R_4 and R_5, which may be the same or different, represents H or (C_1-C_5)-alkyl optionally substituted with hydroxy, (C_1-C_5)-alkoxy or an amino function, or R_4 and R_5 together with the nitrogen atom to which they are attached form a 5- or 6-membered heterocyclic ring optionally containing a further hetero atom; and
n is from 2 to 6,
or an acid addition salt or 1-N-oxide thereof, which process comprises coupling a substituted quinoline of the general formula (II):



(II)

where R_1 and R_2 are as defined above and R_6 represents Cl, Br, OC_6H_4-p-NO_2, 0-(1-N-benzotriazole), 1-N-imidazole or an 0-(2-N-methylpyridinium) salt, or the 1-N-oxide thereof, with a primary alkyl amine of the general formula (III):

$NH_2(CH_2)n^Y$ (III)

where n and Y are as defined above and, if desired, converting a compound of formula (I) into an acid addition salt thereof.

2. A process according to claim 1 where R_1 represents aza, halogen, NO_2, or OCH_3, R_2 represents H, Y represents $N(CH_3)_2$ and n is 2.

3. A process according to claim 1 where R_1 and R_2 represent H, Y represents $N(CH_3)_2$ and n is 2.

4. A process according to claim 1 where R_1 represents 2'-aza, R_2 represents H, Y represents $N(CH_3)_2$ and n is 2.

5. A process according to claim 1 where R_1 represents 3'-aza, R_2 represents H, Y represents $N(CH_3)_2$ and n is 2.

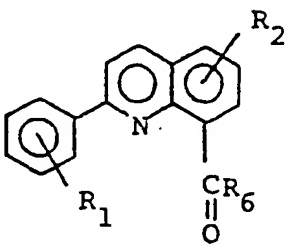
6. A process according to claim 1 where R_1 represents 3'-C1, R_2 represents H, Y represents $N(CH_3)_2$ and n is 2.

7. A process according to claim 1 where R_1 represents 4'-aza, R_2 represents H, Y represents $N(CH_3)_2$ and n is 2.

8. A process according to claim 1 where R_1 represents 4'-Cl, R_2 represents H, Y represents $N(CH_3)_2$ and n is 2.

9. A process according to any one of claims 1 to 8 wherein the coupling reaction of compound (II) with compound (III) is performed in an anhydrous solvent selected from chloroform, dimethylsulphoxide, N-methylpyrrolidone, dichloromethane and dimethylformamide, buffered with a tertiary amine.

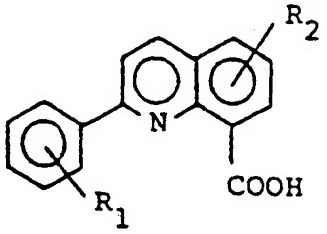
10. A process for the preparation of a compound represented by the general formula (II):



(II)

where R_1 and R_2 are as defined in claim 1, and R_6 represents Cl, Br, OC_6H_4-p-NO_2, 0-(1-N-benzotriazole), 1-N-imidazole, or an 0-(2-N-methylpyridinium) salt, or the 1-N-oxide thereof, which

process comprises reacting a compound of the general formula (X):



(X)

where R_1 and R_2 are as defined in claim 1,or the 1-N-oxide thereof, with a chlorinating agent, a brominating agent, tris(4-nitrophenyl)phosphite, bis(1-N-benzotriazole)carbonate, 1,1'-carbonyl-diimidazole, or a 2-chloro-N-methylpyridinium salt.

11. A process for the preparation of a pharmaceutical composition which comprises bringing into admixture or conjuinction at least one compound of the general formula (I) defined in claim 1, or a pharmaceutically acceptable acid addition salt or 1-N-oxide thereof, and one or more pharmaceutically acceptable carriers or diluents.

12. A process according to claim 11, wherein there is used a compound specified in any one of claims 2 to 8.

13. The use of a compound of the general formula (I) as defined in claim 1, or a pharmaceutically acceptable acid addition salt or 1-N-oxide thereof, for the manufacture of a medicament for use in the treatment of tumours.

14. The use of a compound specified in any one of claims 2 to 8, or a pharmaceutically acceptable acid addition salt or 1-N-oxide thereof, for the manufacture of a medicament for use in the treatment of tumours,

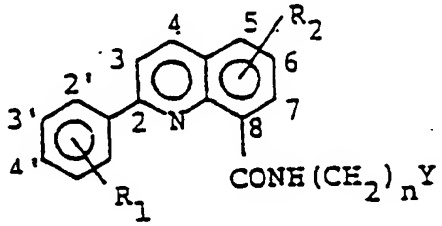
15. The use of a compound of the general formula (I) as defined in claim 1, or a pharmaceutically acceptable acid addition salt or 1-N-oxide thereof, for the manufacture of a medicament for use as an anti-bacterial.

16. The use of a compound specified in any one of claims 2 to 8, or a pharmaceutically acceptable acid addition salt or 1-N-oxide thereof, for the manufacture of a medicament for use as an anti-bacterial.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten: BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Verbindung, wiedergegeben durch die allgemeine Formel (I)



(I)

worin

jeder der Reste R_1 und R_2, die gleich oder verschieden sein können, für H oder eine der Gruppen (C_1- bis C_5-) Alkyl, Halogen, CF_3, CN, SO_2CH_3, NO_2, OH, NH_2, $NHSO_2R_3$, $NHCOR_3$, $NHCOOR_3$, OR_3, SR_3, NHR_3 oder NR_3R_3 steht, worin R_3 für gegebenenfalls mit Hydroxy substituiertes (C_1- bis C_5-)Alkyl, (C_1- bis C_5-)Alkoxy oder eine Aminofunktion steht,oder für den Ersatz eine der Methin-(-CH=)Gruppen in dem jeweiligen carbocyclischen Ring durch eine Aza- (-N=) Gruppe steht oder im Fall von R_1 nur in

den Positionen 2',3' oder 4' für einen Phenylring stehen kann, der gegebenenfalls mit einer der Gruppen (C_1- bis C_5-)Alkyl, Halogen,CF_3,CN, SO_2CH_3, NO_2, OH, NH_2, $NHCOR_3$, $NHCOOR_3$, OR_3, SR_3, NHR_3 oder NR_3R_3 substituiert ist, worin R_3 für gegebenenfalls mit Hydroxy substituiertes (C_1- bis C_5-)Alkyl, (C_1- bis C_5-)Alkoxy oder eine Aminofunktion steht und worin die beiden Gruppen R_3 in NR_3R_3 gleich oder verschieden sein können,
Y für NR_4R_5 steht, worin jeder der Reste R_4 und R_5, die gleich oder verschieden sein können,für H,gegebenenfalls mit Hydroxy substituiertes (C_1- bis C_5-)Alkyl, (C_1- bis C_5-) Alkoxy oder eine Aminofunktion steht oder R_4 und R_5 zusammen mit dem Stickstoffatom, an das sie gebunden sind, einen fünf-oder sechsgliedrigen heterocyclischen Ring bilden, der gegebenenfalls ein weiteres Heteroatom enthält, und
n für 2 bis 6 steht,
oder ein Säureadditionssalz oder 1-N-Oxid der Verbindung.

2. Verbindung nach Anspruch 1, worin R_1 für Aza, Halogen, NO_2 oder OCH_3 steht, R_2 für H steht, Y für $N(CH_3)_2$ steht und n für 2 steht.

3. Verbindung nach Anspruch 1, worin R_1 und R_2 für H stehen, Y für $N(CH_3)_2$ steht und n für 2 steht.

4. Verbindung nach Anspruch 1, worin R_1 für 2'-Aza steht, R_2 für H steht, Y für $H(CH_3)_2$ steht und n für 2 steht.

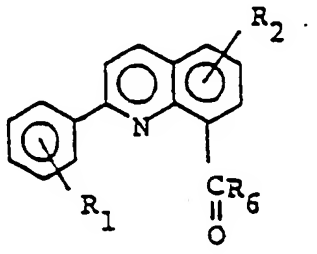
5. Verbindung nach Anspruch 1, worin R_1 für 3'-Aza steht, R_2 für H steht, Y für $N(CH_3)_2$ steht und n für 2 steht.

6. Verbindung nach Anspruch 1, worin R_1 für 3'-Cl steht, R_2 für H steht, Y für $N(CH_3)_2$ steht und n für 2 steht.

7. Verbindung nach Anspruch 1, worin R_1 für 4'-Aza steht, R_2 für H steht, Y für $N(CH_3)_2$ steht und n für 2 steht.

8. Verbindung nach Anspruch 1,worin R_1 für 4'-Cl steht, R_2 für H steht, Y für $N(CH_3)_2$ steht und n für 2 steht.

9. Verfahren zur Herstellung einer Verbindung, die durch die allgemeine Formel (I) wiedergegeben wird, wie sie in Anspruch 1 definiert ist, oder eines Säureadditionssalzes oder eines 1-N-Oxids der Verbindung, wobei das Verfahen das Kuppeln eines substituierten Chinolins der allgemeinen Formel (II)



(II)

worin R_1 und R_2 wie in Anspruch 1 definiert sind und R_6 für Cl, Br, OC_6H_4-p-NO_2, O-(1-N-Benzotriazol), 1-N-Imidazol oder ein O-(2-N-Methylpyridinium-)Salzsteht, oder von dessen 1-N-Oxid mit einem primären Alkylamin der allgemeinen Formel (III)

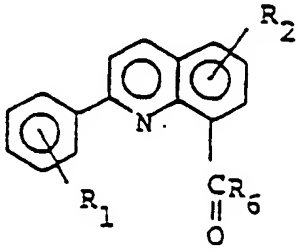
$NH_2(CH_2)_nY$ (III)

worin n und Y wie in Anspruch 1 definiert sind, und - sofern erwünscht - die Umwandlung einer Verbindung der Formel (I) in eines ihrer Säureadditionssalze umfaßt.

10. Verfahren nach Anspruch 9, worin die Kupplungsreaktion von Verbindung (II) mit Verbindung (III) in einem wasserfrein Lösungsmittel durchgeführt wird, das gewählt ist unter Chloroform, Dimediylsulfoxid,

N-Methylpyrrolidon, Dichlormethan und Dimethylformamid, gepuffert mit einem tertiären Amin.

11. Verbindung der allgemeinen Formel (II)



(II)

worin R_1 und R_2 wie in Anspruch 1 definiert sind und R_6 für Cl, Br, OC_6H_4-p-NO_2, O-(1-N-Benzotriazol), 1-N-Imidazol oder ein O-(2-N-Methylpyridinium-)Salz steht, oder deren 1-N-Oxid.

12. Pharmazeutische Zubereitung, die wenigstens eine Verbindung der in Anspruch 1 definierten allgemeinen Formel (I) oder ein pharmazeutisch annehmbares Säureadditionssalz oder 1-N-Oxid dieser Verbindung und einen oder mehrere pharmazeutisch annehmbare Träger oder Verdünnungsmittel umfaßt.

13. Pharmazeutische Zubereitung, die eine Verbindung nach einem der Ansprüche 2 bis 8 oder ein pharmauzeutisch annehmbares Säureadditionssalz oder 1-N-Oxid einer derartigen Verbindung und einen oder mehrere pharmazeutisch annehmbare Träger oder Verdünnungsmittel umfaßt.

14. Verbindung der allgemeinen Formel (I) wie in Anspruch 1 definiert oder ein pharmazeutisch annehmbares Säureadditionssalz oder 1-N-Oxid dieser Verbindung zur Verwendung bei der Behandlung von Tumoren.

15. Verbindung nach einem der Ansprüche 2 bis 8 oder ein pharmazeutisch annehmbares Säureadditionssalz oder 1-N-Oxid einer derartigen: Verbindung zur Verwendung bei der Behandlung von Tumoren.

16. Verbindung der allgemeinen Formel (I) wie in Anspruch 1 definiert oder ein pharmazeutisch annehmbares Säureadditonssalz oder 1-N-Oxid dieser Verbindung zur Verwendung als antibakterielles Mittel.

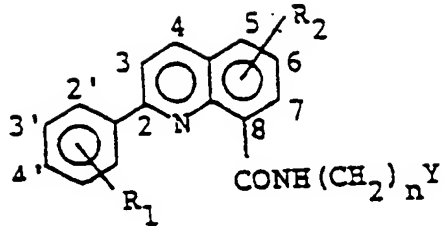
17. Verbindung nach einem der Ansprüche 2 bis 8 oder ein pharmazeutisch annehmbares Säureadditionssalz oder 1-N-Oxid einer derartigen Verbindung zur Verwendung als antibakterielles Mittel.

18. Verwendung einer Verbindung der allgemeinen Formel (I) wie in Anspruch 1 definiert, oder eines pharmarzeutisch annehmbaren Säureadditionssalzes oder 1-N-Oxids dieser Verbindung zur Herstellung eines Arzneimittels zur Verwendung bei der Behandlung von Tumoren.

19. Verwendung einer Verbindung der allgemeinen Formel (I) wie in Anspruch 1 definiert, oder eines pharmazeutisch annehmbaren Säureadditionssalzes oder 1-N-Oxids dieser Verbindung zur Herstellung eines Arzneimittels zur Verwendung als antibakterielles Mittel

Patentansprüche für folgenden Vertragsstaat: AT

1. Verfahren zur Herstellung einer durch die allgemeine Formel (I) wiedergegebenen Verbindung

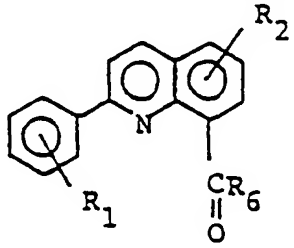


(I)

worin
jeder der Reste R_1 und R_2, die gleich oder verschieden sein können, für H oder eine der Gruppen (C_1- bis C_5-)Alkyl, Halogen, CF_3, CN, SO_2CH_3, NO_2, OH, NH_2, $NHSO_2R_3$, $NHCOR_3$, $NHCOOR_3$, OR_3, SR_3, NHR_3 oder NR_3R_3 steht, worin R_3 für gegebenenfalls mit Hydroxy substituiertes (C_1- bis C_5-)Alkyl, (C_1- bis C_5-)Alkoxy oder eine Aminofunktion steht, oder für den Ersatz einer der Methin- (-CH=)Gruppen in dem jeweiligen carbocyclicschen Ring durch eine Aza-(-N=)Gruppe steht oder im Fall von R_1 nur in den Positionen 2', 3' oder 4'für einen Phenylring stehen kann, der gegebenenfalls mit einer der Gruppen (C_1- bis C_5-)Alkyl, Halogen, CF_3, CN, SO_2CH_3, NO_2, OH, NH_2, $NHCOR_3$, $NHCOOR_3$, OR_3, SR_3, NHR_3 oder NR_3R_3 substituiert ist, worin R_3 für gegebenenfalls mit Hydroxy substituiertes (C_1- bis C_5-)Alkyl,-(C_1- bis C_5-)Alkoxy oder eine Aminofunktion steht und worin die beiden Gruppen R_3 in NR_3R_3 gleich oder verschieden sein können,
Y für NR_4R_5 steht, worin jeder der Reste R_4 und R_5, die gleich oder verschieden sein können, für H, gegebenenfalls mit Hydroxy substituiertes (C_1- bis C_5-)Alkyl, (C_1- bis C_5-) Alkoxy oder eine Aminofunktion steht oder R_4 und R_5 zusammen mit dem Stickstoffatom, an das sie gebunden sind, einen fünf- oder sechsgliedrigen heterocyclischen Ring bilden, der gegebenenfalls ein weiteres Heteroatom enthält, und

n für 2 bis 6 steht,

oder eines Säureadditionssalzes oder 1-N-Oxids der Verbindung, wobei das Verfahren das Kuppeln eines substituierten Chinolins der allgemeinen Formel (II)



(II)

worin R_1 und R_2 wie oben definiert sind und R_6 für Cl, Br, OC_6H_4-p-NO_2, O-(1-N-Benzotriazol), 1-N-Imidazol oder ein O-(2-N-Methylpyridinium-)Salzsteht, oder von dessen 1-N-Oxid mit einem primären Alkylamin der allgemeinen Formel (III)

$NH_2(CH_2)_nY$ (III)

worin n und Y wie oben definiert sind, und - sofern erwünscht - die Umwandlung einer Verbindung der Formel (I) in eines ihrer Säureadditionssalze umfaßt.

2. Verfahren nach Anspruch 1, worin R_1 für Aza, Halogen, NO_2 oder OCH_3 steht, R_2 für H steht, Y für N-$(CH_3)_2$ steht und n für 2 steht.

3. Verfahren nach Anspruch 1, worin R_1 und R_2 für H stehen, Y für $N(CH_3)_2$ steht und n für 2 steht.

4. Verfahren nach Anspruch 1, worin R_1 für 2'-Aza steht, R_2 für H steht, Y für $N(CH_3)_2$ steht und n für 2 steht.

5. Verfahren nach Anspruch 1, worin R_1 für 3'-Aza steht, R_2 für H steht, Y für $N(CH_3)_2$ steht und n für 2 steht.

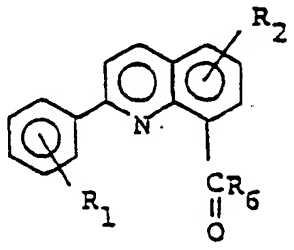
6. Verfahren nach Anspruch 1, worin R_1 für 3'-Cl steht, R_2 für H steht, Y für $N(CH_3)_2$ steht und n für 2 steht.

7. Verfahren nach Anspruch 1, worin R_1 für 4'-Aza steht, R_2 für H steht, Y für $N(CH_3)_2$ steht und n für 2 steht.

8. Verfahren nach Anspruch 1, worin R_1 für 4'-Cl steht, R_2 für H steht, Y für $N(CH_3)_2$ steht und n für 2 steht.

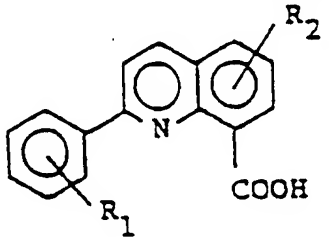
9. Verfahren nach einem der Ansprüche 1 bis 8, worin die Kupplungsreation von Verbindung (II) mit Verbindung (III) in einem wasserfreien Lösungsmittel durchgeführt wird, das gewählt ist unter Chloroform, Dimethylsulfoxid, N-Methylpyrrolidon, Dichlormethan und Dimethylformamid, gepuffert mit einem tertiären Amin.

10. Verfahren zur Herstellung einer durch die allgemeine Formel (II) wiedergegebenen Verbindung



(II)

worin R_1 und R_1 wie in Anspruch 1 definiert sind und R_6 für Cl, Br, OC_6H_4-p-NO_2, O-(1-N-Benzotriazol), 1-N-Imidazol oder ein O-(2-N-Methylpyridinium-)Salzsteht, oder von deren 1-N-Oxid, wobei das Verfahren die Umsetzung einer Verbindung der allgemeinen Formel (X)



(X)

worin R_1 und R_2 wie in Anspruch 1 definiert sind, oder von deren 1-N-Oxid mit einem Chlorierungsmittel, einem Bromierungsmittel, Tris(4-nitrophenyl-)phosphit, Bis(1-N-benzotriazol-)carbonat, 1,1 '-Carbonyldiimidazol oder einem 2-Chlor-N-methylpyridinium-Salz umfaßt.

11. Verfahren zur Herstellung einer pharmazeutischen Zubereitung, welches das In-Mischung-Bringen oder In-Verbindung-Bringen wenigstens einer Verbindung der allgemeinen Formel (I), wie sie in Anspruch 1 definiert ist, oder eines pharmazeutisch annehmbaren Säureadditionssalzes oder 1-N-Oxids dieser Verbindung mit einem oder mehreren pharmazeutisch annehmbaren Trägern oder Verdünnungsmitteln umfaßt.

12. Verfahren nach Anspruch 11, worin eine Verbindung verwendet wird, die in einem der Ansprüche 2 bis 8 spezifiziert ist.

13. Verwendung einer Verbindung der allgemeinen Formel (I) wie in Anspruch 1 definiert oder eines pharmazeutisch annehmbaren Säureadditionssalzes oder 1-N-Oxids dieser Verbindung zur Herstellung eines Arzneimittels zur Verwendung bei der Behandlung von Tumoren.

14. Verwendung einer in einem der Ansprüche 2 bis 8 spezifizierten Verbindung oder eines pharmazeutisch annehmbaren Säurerdditionssalzes oder 1-N-Oxids dieser Verbindung zur Herstellung eines Arzneimittels zur Verwendung bei der Behandlung von Tumoren.

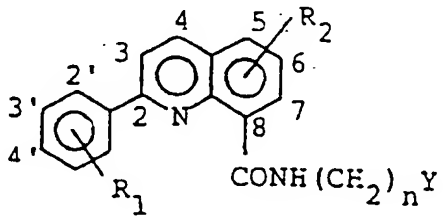
15. Verwendung einer Verbindung der allgemein Formel (I) wie in Anspruch 1 definiert oder eines pharmazeutisch annehmbaren Säureadditionssalzes oder 1-N-Oxids dieser Verbindung zur Herstellung eines Arzneimittels zur Verwendung als antibakterielles Mittel.

16. Verwendung einer in einem der Ansprüche 2 bis 8 spezifizierten Verbindung oder eines pharmazeutisch annehmbaren Säureadditionssalzes oder 1-N-Oxids einer derartigen Verbindung zur Herstellung eines Arzneimittels zur Verwendung als antibakterielles Mittel.

Revendications

Revendications pour les Etats contractants suivants: BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Composé représenté par la formule générale (I)



(I)

où chacun de R_1 et R_2, qui peuvent être identiques ou différents, représente H ou l'un des groupes alkyle en C_1-C_5, halogéno, CF_3, CN, SO_2CH_3, NO_2, OH, NH_2, $NHSO_2R_3$, $NHCOR_3$, $NHCOOR_3$, OR_3, SR_3, NHR_3 ou NR_3R_3 (où R_3 représente un groupe alkyle en C_1-C_5 facultativement substitué par un groupe hydroxyle, alcoxy en C_1-C_5 ou une fonction amino), ou représente le remplacement de l'un des groupes méthyne (-CH=) du noyau carbocyclique correspondant par un groupe aza (-N=) ou, dans le cas de R_1, peut représenter, aux positions 2', 3' ou 4' seulement, un noyau phényle facultativement substitué par l'un des groupes alkyle en C_1-C_5, halogéno, CF_3, CN, SO_2CH_3, NO_2, OH, NH_2, $NHCOR_3$, $NHCOOR_3$, OR_3, SR_3, NHR_3 ou NR_3R_3 (où R_3 représente un groupe alkyle en C_1-C_5 facultativement substitué par un groupe hydroxyle, alcoxy en C_1-C_5 ou une fonction amino et où les deux groupes R_3 de NR_3R_3 peuvent être identiques ou différents) ;

Y représente NR_4R_5, où chacun de R_4 et R_5, qui peuvent être identiques ou différents, représente H ou un groupe alkyle en C_1-C_5 facultativement substitué par un groupe hydroxyle, alcoxy en C_1-C_5 ou une fonction amino, ou bien R_4 et R_5 forment, avec l'atome d'azote auquel ils sont liés, un hétérocycle penta- ou hexagonal contenant facultativement un autre hétéroatome ; et

n est 2 à 6 ;

ou un sel d'addition d'acide ou 1-N-oxyde de ce composé.

2. Composé selon la revendication 1, dans lequel R_1 représente un groupe aza, halogéno, NO_2 ou OCH_3, R_2 représente H, Y représente $N(CH_3)_2$ et n est 2.

3. Composé selon la revendication 1, dans lequel R_1 et R_2 représentent H, Y représente $N(CH_3)_2$ et n est 2.

4. Composé selon la revendication 1, dans lequel R_1 représente 2'-aza, R_2 représente H, Y représente N-$(CH_3)_2$ et n est 2.

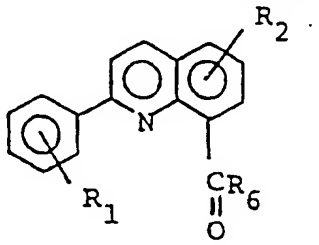
5. Composé selon la revendication 1, dans lequel R_1 représente 3'-aza, R_2 représente H, Y représente N-$(CH_3)_2$ et n est 2.

6. Composé selon la revendication 1, dans lequel R_1 représente 3'-Cl, R_2 représente H, Y représente N-$(CH_3)_2$ et n est 2.

7. Composé selon la revendication 1, dans lequel R_1 représente 4'-aza, R_2 représente H, Y représente N-$(CH_3)_2$ et n est 2.

8. Composé selon la revendication 1, dans lequel R_1 représente 4'-Cl, R_2 représente H, Y représente N-$(CH_3)_2$ et n est 2.

9. Procédé pour la préparation d'un composé représenté par la formule générale (I) telle que définie dans la revendication 1, ou d'un sel d'addition d' acide ou 1-N-oxyde de ce composé, lequel procédé consiste à coupler une quinoléine substituée de formule générale (II) :



(II)

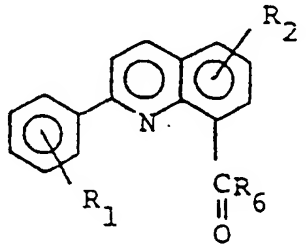
où R_1 et R_2 sont tels que définis dans la revendication 1 et R_6 représente Cl Br, OC_6H_4-*p*-NO_2, O-(1-N-benzotriazole), 1-N-imidazole ou un sel de O-(2-N-méthylpyridinium), ou son 1-N-oxyde, avec une alkylamine primaire de formule générale (III) :

$NH_2(CH_2)_nY$ (III)

où n et Y sont tels que définis dans la revendication 1 et, facultativement, à convertir un composé de formule (I) en un sel d'addition d'acide de celui-ci.

10. Procédé selon la revendication 9, dans lequel la réaction de couplage du composé (II) avec le composé (III) est effectuée dans un solvant anhydre choisi parmi le chloroforme, le diméthylsulfoxyde, la N-méthylpyrrolidone, le dichlorométhane et le diméthylformamide, tamponné avec une amine tertiaire.

11. Composé représenté par la formule générale (II)



(II)

où R_1 et R_2 sont tels que définis dans la revendication 1, et R_6 représente Cl, Br, OC_6H_4-*p*-NO_2, O-(1-N-benzotriazole), 1-N-imidazole ou un sel de O-(2-N-méthylpyridinium), ou son 1-N-oxyde.

12. Composition pharmaceutique qui comprend au moins un composé de formule générale (I) définie dans la revendication 1, ou un sel d'addition d'acide pharmaceutiquement acceptable ou 1-N-oxyde de ce composé, et un ou plusieurs supports ou diluants pharmaceutiquement acceptables.

13. Composition pharmaceutique qui comprend un composé selon l'une quelconque des revendications 2 à 8, ou un sel d'addition d'acide pharmaceutiquement acceptable ou 1-N-oxyde de ce composé, et un ou plusieurs supports ou diluants pharmaceutiquement acceptables.

14. Composé de formule générale (I) telle que définie dans la revendication 1, ou un sel d'addition d'acide pharmaceutiquement acceptable ou 1-N-oxyde de ce composé, pour son utilisation dans le traitement de tumeurs.

15. Composé selon l'une quelconque des revendications 2 à 8, ou sel d'addition d'acide pharmaceutiquement acceptable ou 1-N-oxyde de ce composé, pour son utilisation dans le traitement de tumeurs.

16. Composé de formule générale (I) telle que définie dans la revendication 1, ou un sel d'addition d'acide pharmaceutiquement acceptable ou 1-N-oxyde de ce composé, pour son utilisation comme agent antibactérien.

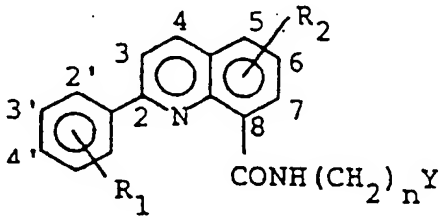
17. Composé selon l'une quelconque des revendications 2 à 8, ou un sel d'addition d'acide pharmaceutiquement acceptable ou 1-N-oxyde de ce composé, pour son utilisation comme agent antibactérien.

18. Utilisation d'un composé de formule générale (I) telle que définie dans la revendication 1, ou d'un sel d'addition d'acide pharmaceutiquement acceptable ou 1-N-oxyde de ce composé, pour la fabrication d'un médicament à utiliser dans le traitement de tumeurs.

19. Utilisation d'un composé de formule générale (I) telle que définie dans la revendication 1, ou d'un sel d'addition d'acide pharmaceutiquement acceptable ou 1-N-oxyde de ce composé, pour la fabrication d'un médicament à utiliser comme antibactérien.

Revendications pour l'Etat contractant suivant: AT

1. Procédé pour la préparation d'un composé représenté par la formule générale (I) :



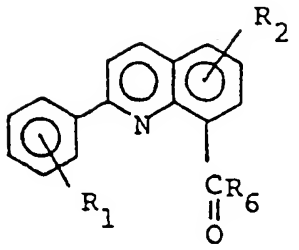
(I)

où chacun de R_1 et R_2, qui peuvent être identiques ou différents, représente H ou l'un des groupes alkyle en C_1-C_5, halogéno, CF_3, CN, SO_2CH_3, NO_2, OH, NH_2, $NHSO_2R_3$, $NHCOR_3$, $NHCOOR_3$, OR_3, SR_3, NHR_3 ou NR_3R_3 (où R_3 représente un groupe alkyle en C_1-C_5 facultativement substitué par un groupe hydroxyle, alcoxy en C_1-C_5 ou une fonction amino), ou représente le remplacement de l'un des groupes méthyne (-CH=) du noyau carbocyclique correspondant par un groupe aza (-N=) ou, dans le cas de R_1, peut représenter, aux positions 2', 3' ou 4' seulement, un noyau phényle facultativement substitué par l'un des groupes alkyle en C_1-C_5, halogéno, CF_3, CN, SO_2CH_3, NO_2, OH, NH_2, $NHCOR_3$, $NHCOOR_3$, OR_3, SR_3, NHR_3 ou NR_3R_3 (où R_3 représente un groupe alkyle en C_1-C_5 facultativement substitué par un groupe hydroxyle, alcoxy en C_1-C_5 ou une fonction amino et où les deux groupes R_3 de NR_3R_3 peuvent être identiques ou différents) ;

Y représente NR_4R_5, où chacun de R_4 et R_5, qui peuvent être identiques ou différents, représente H ou un groupe alkyle en C_1-C_5 facultativement substitué par un groupe hydroxyle, alcoxy en C_1-C_5 ou une fonction amino, ou bien R_4 et R_5 forment, avec l'atome d'azote auquel ils sont liés, un hétérocycle penta- ou hexagonal contenant facultativement un autre hétéroatome ; et

n est 2 à 6 ;

ou d'un sel d'addition d'acide ou 1-N-oxyde de ce composé, lequel procédé consiste à coupler une quinoléine substituée de formule générale (II) :



(II)

où R_1 et R_2 sont tels que définis ci-dessus et R_6 représente Cl, Br, OC_6H_4-*p*-NO_2, O-(1-N-benzotriazole), 1-N-imidazole ou un sel de O-(2-N-méthylpyridinium), ou son 1-N-oxyde, avec une alkylamine primaire de formule générale (III) :

$NH_2(CH_2)_nY$ (III)

où n et Y sont tels que définis ci-dessus et, facultativement, à convertir un composé de formule (I) en un sel d'addition d'acide de celui-ci.

2. Procédé selon la revendication 1, dans lequel R_1 représente un groupe aza, halogéno, NO_2 ou OCH_3, R_2 représente H, Y représente $N(CH_3)_2$ et n est 2.

3. Procédé selon la revendication 1, dans lequel R_1 et R_2 représentent H, Y représente $N(CH_3)_2$ et n est 2.

4. Procédé selon la revendication 1, dans lequel R_1 représente 2'-aza, R_2 représente H, Y représente N-$(CH_3)_2$ et n est 2.

5. Procédé selon la revendication 1, dans lequel R_1 représente 3'-aza, R_2 représente H, Y représente N-$(CH_3)_2$ et n est 2.

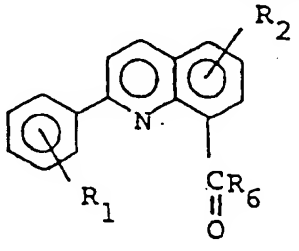
6. Procédé selon la revendication 1, dans lequel R_1 représente 3'-Cl, R_2 représente H, Y représente N-$(CH_3)_2$ et n est 2.

7. Procédé selon la revendication 1, dans lequel R_1 représente 4'-aza, R_2 représente H, Y représente N-$(CH_3)_2$ et n est 2.

8. Procédé selon la revendication 1, dans lequel R_1 représente 4'-Cl, R_2 représente H, Y représente N-$(CH_3)_2$ et n est 2.

9. Procédé selon l'une quelconque des revendications 1 à 8, dans lequel la réaction de couplage du composé (II) avec le composé (III) est effectuée dans un solvant anhydre choisi parmi le chloroforme, le diméthylsulfoxyde, la N-méthylpyrrolidone, le dichlorométhane et le diméthylformamide, tamponné avec une amine tertiaire.

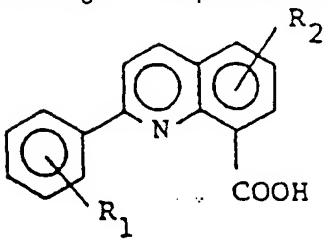
10. Procédé pour la préparation d'un composé représenté par la formule générale (II) :



(II)

où R_1 et R_2 sont tels que définis dans la revendication 1 et R_6 représente Cl, Br, OC_6H_4-*p*-NO_2, O-(1-N-benzotriazole), 1-N-imidazole ou un sel de O-(2-N-méthylpyridinium), ou de son 1-N-oxyde, lequel

procédé consiste à faire réagir un composé de formule générale (X) :



(X)

où R_1 et R_2 sont tels que définis dans la revendication 1, ou son 1-N-oxyde, avec un agent de chloration, un agent de bromation, le phosphite de tris(4-nitrophényle), le carbonate de bis(1-N-benzotriazole), le 1,1'-carbonyldiimidazole ou un sel de 2-chloro-N-méthylpyridinium.

11. Procédé pour la préparation d'une composition pharmaceutique qui consiste à mettre en mélange ou en association au moins un composé de formule générale (I) définie dans la revendication 1, ou un sel d'addition d'acide pharmaceutiquement acceptable ou 1-N-oxyde de ce composé, et un ou plusieurs supports ou diluants pharmaceutiquement acceptables.

12. Procédé selon la revendication 11, dans lequel est utilisé un composé spécifié dans l'une quelconque des revendications 2 à 8.

13. Utilisation d'un composé de formule générale (I) telle que définie dans la revendication 1, ou d'un sel d'addition d'acide pharmaceutiquement acceptable ou 1-N-oxyde de ce composé, pour la fabrication d'un médicament à utiliser dans le traitement de tumeurs.

14. Utilisation d un composé spécifié dans l'une quelconque des revendications 2 à 8, ou d'un sel d'addition d'acide pharmaceutiquement acceptable ou 1-N-oxyde de ce composé, pour la fabrication d'un médicament à utiliser dans le traitement de tumeurs.

15. Utilisation d'un composé de formule générale (I) telle que définie dans la revendication 1, ou d'un sel d'addition d'acide pharmaceutiquement acceptable ou 1-N-oxyde de ce composé, pour la fabrication d'un médicament à utiliser comme antibactérien.

16. Utilisation d un composé spécifié dans l'une quelconque des revendications 2 à 8, ou d'un sel d'addition d'acide pharmaceutiquement acceptable ou 1-N-oxyde de ce composé, pour la fabrication d'un médicament à utiliser comme antibactérien.